Title: REPORTING OF SERIOUS ADVERSE EVENTS **Version No.:** 1.9

SOP No.: RR-408 **Effective Date:** January 21, 2025

1. Purpose

This policy describes the documentation and reporting requirements for serious adverse events (SAE) as part of the continuing review that occurs after approval and prior to review for renewal of IRB approval.

2. Policy

2.1 SAE reporting starts as soon as the participant begins investigational treatment/intervention.

2.1.1 Prior to starting investigational treatment/intervention, SAE reporting is required if the event is related to any protocol test or procedure. The event must be reported within 5 calendar days of learning of the event.

2.2 SAEs requiring submission to the HRPP Office must be reported within 5 calendar days of learning of the event. SAEs not requiring submission to the HRPP Office must be saved in the regulatory binder within 30 calendar days of learning of the event.

2.3 All safety information correspondence that warrants a change to the conduct of the protocol or informed consent must be submitted to the HRPP Office via the PIMS Safety Information Form within 5 calendar days of receipt of correspondence. Otherwise, the correspondence must be filed in the regulatory binder.

2.4 If a participant is experiencing an SAE at the time of withdrawal from protocol, the investigator should continue to follow the participant for optimal medical care and safety reporting purposes.

2.5 Sites relying on the MSK IRB and sites participating on MSK-held IND/IDE protocols must adhere only to the requirements outlined in sections 3.1 and 3.2. The MSK study team responsible for working with the participating site must submit the SAE in PIMS if a site does not have access to the PIMS SAE submission module.

3. Specific Procedures

3.1 Definitions

Unless otherwise specified in the protocol/Single Patient Use (SPU) treatment plan, a **Serious Adverse Event (SAE)** is an event that results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization (Note: a hospital admission for a planned procedure/disease treatment is not considered an SAE)
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Any other event specified in the protocol to be an SAE

Attributions:

Unrelated: The AE is clearly NOT related to the intervention
Unlikely: The AE is doubtfully related to the intervention
Possible: The AE may be related to the intervention
Probable: The AE is likely related to the intervention
Definite: The AE is clearly related to the intervention

Expected and Unexpected Events:

Expected: Any experience previously reported (in nature, severity, or incidence) in the current Investigator's Brochure or general investigational plan
Unexpected: Any experience *not previously reported* (in nature, severity, or incidence) in the current Investigator's Brochure or general investigational plan

3.2 Reporting: Serious Adverse Events (SAEs)

3.2.1 Format

SAEs must be entered in PIMS unless an exception has been granted by the HRPP Office.

3.2.2 Submission

The PI must submit all PIMS SAE reports. In order to abide by the reporting timeline, the Co-PI or participating investigator may submit the report if the PI is unavailable.

3.2.3 Timelines

a) The following must be reported to the HRPP Office within 5 calendar days of learning of the event:
   - For MSK-held IND/IDE protocols: All SAEs
   - Unexpected and related (possible, probable, or definite) SAEs
   - Single Patient Use (SPU) SAEs

b) All other SAEs must be filed in the regulatory binder within 30 calendar days of learning of the event.

c) Exceptions to the Reporting Timeline:
   - When an event is unexpected, related, and indicates participants or others are at increased risk of harm, the Principal Investigator is required to report the SAE as soon as possible and within 5 calendar days of learning of the event as per MSK IRB SOP RR-409.

d) The date of learning of the event is defined as follows:
   - Occurred at an MSK facility and/or participating/relying site facility: the start date of the event.
   - Occurred outside of above noted facilities: date MSK/participating/relying site learns of the event

3.2.4 Reporting Period

Unless otherwise specified in the protocol/SPU, SAE reporting ends 30 days after the participant's last protocol treatment/intervention (e.g. drug administration on a drug protocol, questionnaire on a QOL protocol, counseling session).

An SAE that occurs after the 30-day period that is unexpected and related (possible, probable, or definite) must be reported to the HRPP Office.

3.2.5 Other Reporting Requirements

a) MSK-held IND/IDE protocols: The HRPP Office is responsible for informing the MSK IND Office of any SAE that requires reporting to the FDA per FDA 21 CFR 312.32. It is the responsibility of the IND Office to submit SAEs directly to the FDA, if needed.
b) Gene-transfer protocols: It is the responsibility of the investigator to report applicable adverse events to the NIH Office of Biotechnology (OBA) per the OBA Guidelines.
c) Unanticipated adverse device effects must be reported to the HRPP Office via the PIMS SAE form within 5 calendar days of learning of the event. An unanticipated adverse device effect is defined as any unexpected serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an FDA regulated device.
d) Pregnancy: If a protocol participant or their partner becomes pregnant while the participant is actively on study or in follow-up, the HRPP Office must be notified. The HRPP Office will advise on if any additional action is needed. Pregnancies must be reported to outside entities (e.g., sponsor, funder, external IRB of record) as outlined in the protocol.

3.3 Reporting: Safety Information Correspondence

3.3.1 Format

Safety information correspondence must be submitted to the HRPP Office in PIMS via the Safety Information Form. Reportable safety correspondence includes, but is not limited to, Dear Investigator Letters, and outside safety reports (e.g. SUSAR).

3.3.2 Submission

The MSK PI must submit all Safety Information Forms. In order to abide by the reporting timeline, the MSK Co-PI may submit the report if the PI is unavailable.

3.3.3 Timelines

a) Safety information correspondence that warrants a change to the conduct of the protocol must be submitted within 5 calendar days of receipt of such correspondence. Examples include changes in the protocol and/or informed consent process/document due to a safety reason, such as revisions to the inclusion/exclusion criteria, the addition of new safety monitoring requirement(s), the addition of a new risk; and/or hold on new participant enrollment or current research activity for safety reasons.
    - NCI Action Letters do not require submission to the HRPP Office via the Safety Information Form if they are being submitted as an amendment.
b) Safety correspondence that does not meet the criteria above, as assessed by the MSK PI, must be filed in the regulatory binder. Documentation of the MSK PI's assessment should be maintained.
    - For NCI safety reports, the documentation included in the email notification from NCI can serve as documentation of PI assessment.

3.3.4 Reporting Period

a) The above noted policy starts as soon as a protocol is approved by the IRB.
b) When safety correspondence is received prior to IRB protocol approval:
    - If it does not meet the above criteria, keep the correspondence in the regulatory binder.
    - If it meets the above criteria, incorporate necessary changes into the protocol documents.

c) Once a protocol is closed, no action is required. However, if the protocol sponsor indicates the safety correspondence should be forwarded to the HRPP, it must be sent to the HRPP Office.

3.4 General Requirements

3.4.1 The HRPP Office will review events if an investigator is unsure whether the event should be reported, and the HRPP Office will review such reports to determine whether the event meets the threshold for reporting.

3.4.2 In rare circumstances when an investigator cannot submit an SAE via PIMS, initial reports may be accepted by other means such as e-mail or phone, with a written follow up report.

3.4.3 The Unanticipated Problem (UP) Review Team may review a report and make an assessment on whether the event is (1) unanticipated (2) related or possibly related to participation in the research and (3) suggests that the research places subjects or others at increased risk of harm than was previously known or recognized. If yes to all, the problem is considered a potential unanticipated problem involving risks to participants or others. UPs will be reviewed by the convened IRB in accordance with MSK IRB SOP RR-409 and will be reported according to MSK IRB SOP CO-602.

3.4.4 **Commercial Agents Only**: All SAEs that occur on an IRB approved research protocol where the participant received only commercial agents are reportable per section 3.2.

3.4.5 **MSK Investigator-Initiated Trials**: SAEs that require HRPP reporting must be submitted to the HRPP Office before sharing with drug suppliers or any other outside entity unless otherwise outlined in the protocol.

3.4.6 **Prospective minimal risk protocols** (e.g. data, biological specimen collection/use, Quality of Life) may request to waive the reporting of some serious adverse events (e.g., deaths on an End-of-Life questionnaire study) provided the following are met:

- Protocol outlines the types of SAE reporting that would be waived
- These are events that are completely unrelated to protocol
- Events that could be related to protocol intervention are outlined in the protocol and must be reported according to section 3.2.

3.4.7 **Weekend/Holiday SAEs**: For SAEs that occur outside of regular business hours (i.e., a holiday OR after 5pm on Friday through 9am on Monday), the 24-hour timeline for reporting SAEs to outside entities begins at the start of the next business day.

3.5 Other Reportable Events

3.5.1 Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).

3.5.2 Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency.

3.5.3 Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.

3.5.4 Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.

4. Applicable Regulations and References

- 21 CFR 312.32
- 21 CFR 812.150
- Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection, U.S. Department of Health and Human Services, Food and Drug Administration, Office of the Commissioner (OC), January 2009
- Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, Office of Human Research Protection (OHRP), January 2007
- MSK IRB SOPs GA-106, CO-602, RR-409

Revision History

Revision	Effective Date	Reason for Change
1.0	6/15/09	New
1.1	9/24/12	• Clarified reporting timelines for SAE occurring outside of MSK to within 5 days of learning of the event. • Added specific reporting requirements for MCT trials when MSK is the data coordinating center.
1.2	6/8/15	• Physician in chief changed to Paul Sabbatini, MD • Updated position titles for Ann Rodavitch and Collette Houston. • Formatting, branding. • Clarified due date for SAE reports. • Outside safety report requirements and timeline for submission: Only events that are unexpected, related, serious AND warrant a significant change to the conduct of the study must be submitted to the IRB within 7 calendar days of learning of the event. • Updated the definition of an SAE and an outside safety report. • Added additional reporting requirements for Multicenter Trials when MSK is the Data Coordinating Center. • Clarified that SPU SAEs must be reported on the SAE Report Form for Single Patient Use. • Added applicable regulations and references.
1.3	2/29/16	• Renumbered to RR-408 (formerly RR-403). • Updated Signature page, MSK branding, formatting. • Updated types of SAEs that are IRB reportable • Clarified the reporting period for OSRs. • Updated the language in the Multicenter Trials section to be consistent with new policy language. • Added reporting requirements for MSK-held IND/IDE and gene-transfer protocols.
1.4	4/25/18	• 2.1 Added LAR • 3.1 Updated definition of SAE to include any other event specified in the protocol to be an SAE • 3.2.2 Removed sentence regarding IRB notification of PI leave • 3.2.3 Clarified CTEP-AERs reporting requirements; Clarified that an outside SAE is an SAE that occurs outside of an MSK facility

		• 3.2.4 Clarified that SAEs occurring after the 30-day mark must be reported to the IRB if unexpected and related • 3.3 Replaced OSR Form with Safety Information Form; • 3.3.1 Clarified "reportable" OSRs and added reference to 3.3.3 • 3.3.2 Removed sentence regarding IRB notification of PI leave • 3.3.3b Clarified the PI's role in the assessment and documentation for non-IRB reportable OSRs that are filed in the regulatory binder • 3.4.10 Added guidance for SAEs that start outside of normal business hours • 3.5.8 Added reporting requirements for SAEs that are related to protocol-mandated test or procedure
1.5	12/10/18	• 2.1 Changed SAE reporting start date to when the participant begins investigational treatment/intervention • 2.1.1 Added • Replaced IRB with HRPP Office throughout the SOP • 3.2.1 Changed the format from the CRDB SAE Form to PIMS • 3.2.2 Revised this section from PI Signature to Submission; removed the requirement for an investigator to sign the SAE report • 3.2.3a Removed "All events requiring submission in CTEP-AERs" • 3.2.3d Defined "date of learning of the event"; collapsed previous section 3.2.3e into this section • 3.2.5a Replaced SAE Office with IND Office as the party responsible for submitting SAEs to the FDA • 3.4.2 Clarified that initial reports will be accepted outside of PIMS in rare circumstances when an investigator cannot submit in PIMS • 3.4.6 Updated HRPP reporting requirement for participating site SAEs to include only SAEs under an MSK-held IND/IDE trial • 3.4.7 Clarified that this requirement is for prospective minimal risk trials • 3.4.8 Updated SPU SAE requirements such that all SAEs occurring under an SPU must be reported to the HRPP Office
1.6	5/11/20	• 2.1.1 Added reporting timeframe • 3.2.3a Added SPU SAEs • 3.2.3c Updated to align with IRB SOP RR-409 • 3.3.1 Updated to note that SIFs must be submitted in PIMS • 3.3.2 Update section from "PI Signatures" to "Submission" to reflect SIF submission in PIMS • Former section 3.4.8 (Single Patient Use) was removed as SPU submissions are now incorporated into section 3.2.3a • Former section 3.4.9 (Protocol deviations: If a protocol deviation involves an SAE, report the deviation to the HRPP office and submit a copy of the deviation to the HRPP office with the SAE report was removed • 3.4.8 Updated to note that this section applies to the 24-hour timeline for reporting SAEs to outside entities • 3.5.8 Removed since the information was added to section 2.1.1
1.7	9/20/21	• 2.3 Updated to include all safety information correspondence, not only outside safety reports • 2.4 Added policy statement regarding participants experiencing an SAE at the time withdrawal from protocol • 2.5 Added policy statement regarding sites relying on the MSK IRB and sites participating on MSK-held IND/IDE protocols; former policy statement regarding multicenter trials when MSK is the data coordinating center was removed.

		• 3.1 Removed definition of outside safety report • 3.2.3a Removed grade 5 (fatal) events from the list of events requiring submission to HRPP; HRPP will still receive unexpected/related grade 5 events • 3.2.3c Updated 5 business days to 5 calendar days to align with MSK IRB SOP RR-409 • 3.2.5c Unanticipated adverse device effect language was simplified and moved from section 3.5.6 to this section • 3.3 Updated section to include all safety information correspondence and to align with current Safety Information Form requirements • 3.4.5 Added “unless otherwise outlined in the protocol” to align with current practice • Former section 3.4.6 (Multicenter trials when MSK is the data coordinating center) was removed • 3.5 Removed “Any AE that would cause a modification to the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects” and “A paper is published from another study that shows that an arm of your research study is of no therapeutic value” as this is covered in MSK IRB SOPs FO-304 and RR-405, respectively.
1.8	1/23/23	• Removed “Ongoing Continuing Review” from the title • 2.5 Updated to include 3.1; clarified that sites have to adhere only to sections 3.1 and 3.2 • 3.1 Updated SAE definition to include “Unless otherwise specified in the protocol/Single Patient Use (SPU) treatment plan” • 3.2.5d Added section for Pregnancy reporting • 3.3.3 Updated to note MSK PI
1.9	1/21/25	• 3.2.5a Updated FDA regulation